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# The Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score as an Independent Prognostic Factor for Esophageal Cancer Patients who Received Curative Treatment

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## Abstract

*Background/Aim:* Esophageal cancer (EC) is a malignant tumor with poor prognosis. Prognostic factors that may be used in the treatment and management of EC are important. The purpose of this study was to evaluate the impact of the hemoglobin, albumin, lymphocyte, and platelet (HALP) score on the long-term oncological prognosis of patients with EC who have undergone curative treatment.

*Patients and Methods:* Patients with EC who underwent curative resection at Yokohama City University between 2000 and 2020 were included. Clinical data were retrospectively retrieved from medical records and analyzed. The HALP score was determined as follows: HALP=[hemoglobin (g/l)×albumin (g/l)×lymphocytes (/l)]/platelets (/l). Kaplan-Meier method and Cox regression model were used to assess the overall (OS) and recurrence-free survival (RFS) and to evaluate the prognostic value of the HALP score.

*Results:* In total, 180 patients were included in this study. They were classified into the HALP-low (n=110) and HALP-high (n=70) groups using a cutoff value of 40. The 5-year OS rate was 46.9% in the HALP-low group and 66.0% in the HALP-high group ($p$=0.012). The 5-year RFS rate was 31.1% in the HALP-low group and 51.4% in the HALP-high group ($p$=0.006). The HALP score was found to be an independent prognostic factor for OS [odds ratio (OR)=1.954, 95% confidence interval (CI)=1.157-3.299, $p$=0.012] and RFS (OR=1.852, 95% CI=1.197-2.866, $p$=0.006).

*Conclusion:* The HALP score is a factor that predicts the oncological prognosis in patients with EC who have undergone radical resection.

**Keywords:** HALP, esophageal cancer, survival, esophagectomy, prognostic factor

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## Introduction

Esophageal cancer is the 11th most common cancer diagnosed worldwide and the 7th most common cause of cancer death. It is estimated that 511,000 new cases will be diagnosed, and 445,000 people will die from the disease in 2022 (1). The standard treatment for locally advanced EC is perioperative adjuvant therapy and surgical resection. Despite advances in the treatment of EC, the overall 5-year survival rate after the resection of EC remains poor (2, 3). Therefore, to improve the prognosis of patients with EC, it is necessary to identify reliable prognostic factors and to provide appropriate treatment using these prognostic factors.

In cancer patients, immunity and nutritional status are important prognostic factors (4). Nutritional deficiencies due to chronic catabolism, bone marrow suppression, and immunosuppression due to adjuvant treatment have a significant impact on the patient prognosis (5, 6). EC is often treated with neoadjuvant chemotherapy (NAC) as a standard treatment, and there is a high risk of immunosuppression and cachexia (7).

Various prognostic factors have been reported for EC (8-10). Recently, several prognostic factors related to inflammation and nutrition have been reported. Inflammation-based factors include the neutrophil-to-lymphocyte ratio (NLR) (11), platelet-to-lymphocyte ratio (PLR) (12), lymphocyte-to-monocyte ratio (LMR) (13), and systemic immune inflammation index (SII) (14). Nutrition-based factors include the prognostic nutritional index (PNI) (15), Glasgow prognostic score (GPS) (16), and modified Glasgow prognostic score (mGPS) (17).

In 2015, Chen *et al*. reported that the preoperative hemoglobin, albumin, lymphocyte and platelet (HALP) score was an independent prognostic factor in patients with gastric cancer (18). The HALP score reflects the nutritional and immune status and is useful for predicting oncological outcomes. Few studies have evaluated the clinical impact of the HALP score in relation to EC (19-21).

This study aimed to evaluate the clinical impact of the HALP score in patients with EC who had undergone curative treatment and to clarify the potential application of the HALP score as a prognostic factor.

## Patients and Methods

*Patients.* Patients who underwent curative resection for EC at Yokohama City University between 2000 and 2020 were selected based on their medical records. Patients who met the following criteria were included in the study: (i) histologically confirmed squamous cell carcinoma; (ii) clinical stage 0-III disease, defined according to the 12th edition of the general rules of the Japanese Esophageal Cancer Association (22); (iii) esophagectomy after preoperative chemoradiotherapy or chemotherapy and curative esophagectomy as the primary treatment for EC; and (iv) complete (R0) resection of EC.

*Surgery and adjuvant treatment.* All the patients in the present study underwent esophagectomy with either 2- or 3-field lymphadenectomy. Patients with pathological stage II or III disease received postoperative adjuvant chemotherapy.

*Determination of the hemoglobin, albumin, lymphocyte and platelet (HALP) score.* The HALP score was determined as follows:
HALP=[hemoglobin (g/l)×albumin (g/l)×lymphocytes (/l)]/platelets (/l). These blood collection data were collected before treatment.

*Follow-up*. Follow-up evaluations were conducted in outpatient clinics, and patients underwent blood tests, including measurement of tumor markers, and physical examinations at least every 3 months for 5 years. In addition, computed tomography (CT) scans were performed once within 3 months of surgery and once every 6 months until 5 years after surgery.

*Statistical analysis.* Data are presented as counts and percentages. HALP and clinicopathological factors were analyzed between the two patient groups using the chi-

Table I. *Patient characteristics in total patients and stratified by HALP score.*

| Characteristics | All patients (%) (n=180) | Patients with HALP index ≤40 (n=110) | Patients with HALP index >40 (n=70) | *p*-Value |
|---|---|---|---|---|
| Age (years) | | | | 0.227 |
| <70 | 95 (52.8%) | 62 (34.4%) | 33 (18.3%) | |
| ≥70 | 85 (47.2%) | 48 (26.7%) | 37 (20.6%) | |
| Sex | | | | 0.749 |
| Male | 155 (86.1%) | 94 (52.2%) | 61 (33.9%) | |
| Female | 25 (13.9%) | 16 (8.9%) | 9 (5.0%) | |
| Site of tumor | | | | 0.896 |
| Upper | 53 (29.4%) | 32 (17.8%) | 21 (11.7%) | |
| Middle/Lower | 127 (70.6%) | 78 (43.3%) | 49 (27.2% | |
| T status | | | | **0.025** |
| T1 | 79 (43.9%) | 41 (22.8%) | 38 (21.1%) | |
| T2 to T3 | 101 (56.1%) | 69 (38.3%) | 32 (17.8%) | |
| Lymph node metastasis | | | | 0.349 |
| Negative | 95 | 55 (30.6%) | 40 (22.2%) | |
| Positive | 85 | 55 (30.6%) | 30 (16.7%) | |
| Lymph-vascular invasion | | | | 0.637 |
| Negative | 58 (32.2%) | 34 (18.9%) | 24 (13.3%) | |
| Positive | 122 (67.8%) | 76 (42.2%) | 46 (25.6%) | |
| Postoperative surgical complications | | | | 0.381 |
| No | 53 (29.4%) | 75 (41.7%) | 52 (28.9%) | |
| Yes | 127 (70.6%) | 35 (19.4%) | 18 (10.0%) | |
| Neoadjuvant chemotherapy | | | | **<0.001** |
| No | 92 (51.1%) | 67 (37.2%) | 25 (13.9%) | |
| Yes | 88 (48.9%) | 43 (23.9%) | 45 (25.0%) | |

HALP: hemoglobin, albumin, lymphocyte, platelet score. Statistically significant *p*-values are shown in bold.

squared test. The Kaplan-Meier method was used to generate curves for overall and recurrence-free survival and logrank test was used to compare the survival curves between the two groups. A Cox proportional hazards model was used for the univariable and multivariable survival analyses. Statistical significance was set at $p<0.05$. SPSS (v27.0 Win; IBM, Armonk, NY, USA) was used to perform all the statistical analyses.

*Ethical approval.* This study was approved by the Institutional Review Board of Yokohama City University.

## Results

*Patient characteristics.* This study included 180 patients (male, n=155; female, n=25) with a median age of 70 years. The 3- and 5- year OS was reduced in patients with HALP score ≤40 compared to the OS in patients with HALP >40 (55.1% and 46.9% *vs*. 75.1% and 66.0%, respectively, $p=0.003$ for both comparisons). Thus, we set the cut off value of HALP score at 40 in the present study. According to the above cutoff values, the 180 patients in this study were divided into two groups: HALP-low [HALP<40; n=110 (61.1%)] and HALP-high [HALP≥40; n=70 (38.9%)]. The patient backgrounds of the two groups (HALP-high *vs*. HALP-low) were compared and no difference was found in terms of age (43.4 *vs*. 52.9%, $p=0.227$), male to female ratio ($p=0.749$), percentage of cases with tumor located in the upper esophagus ($p=0.896$), rate of lymph node metastasis ($p=0.349$), rate of lymphovascular invasion ($p=0.637$), and postoperative surgical complications ($p=0.381$). However, the T status of the HALP-low group was higher than that of

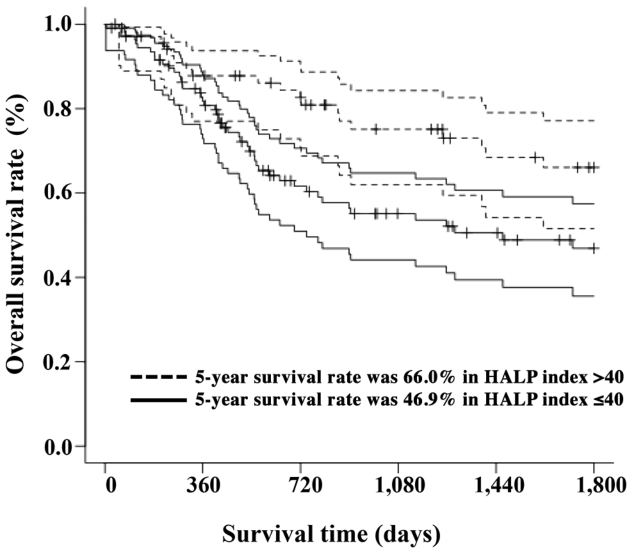


Figure 1. *Overall survival of esophageal cancer patients in the HALP-high and HALP-low groups. HALP: Hemoglobin, albumin, lymphocyte and platelet.*

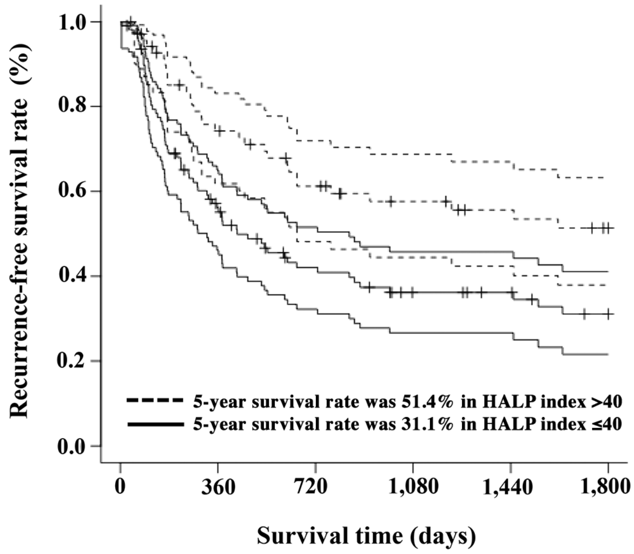


Figure 2. *Recurrence-free survival of esophageal cancer patients in the HALP-high and HALP-low groups. HALP: Hemoglobin, albumin, lymphocyte and platelet.*

the HALP-high group in patients (62.7% *vs.* 45.7%, *p*=0.025). In addition, the HALP-high group showed a higher rate of neoadjuvant chemotherapy (NAC) induction than the HALP-low group (39.1% *vs.* 64.3%, *p*<0.001) (Table I).

*Overall survival.* There was a significant difference between the high and low HALP groups in terms of overall survival. The 5- year OS rate was 66.0% in the HALP-high group and 46.9% in the HALP-low group (*p*=0.012) (Figure 1). Each clinicopathological factor was analyzed regarding OS and its usefulness as a prognostic factor was considered (Table II). In univariable Cox proportional hazards analyses for OS, T status, lymph node metastasis, HALP index, and lymphovascular invasion were identified as significant prognostic factors. In addition, according to the multivariable Cox proportional hazards analysis for OS, the HALP score was identified as an independent prognostic factor [odds ratio (OR)=1.954, 95% confidence interval (CI)=1.157-3.299, *p*=0.012]. Similarly, T status, lymph node metastasis, and lymph-vascular invasion were identified as prognostic factors in multivariable analysis.

*Recurrence-free survival (RFS).* There was also a significant difference between the HALP high and low groups in terms of RFS. The 5- year RFS rates were 51.4% in the HALP-high group and 31.1% in the HALP-low group (*p*=0.006) (Figure 2). In the univariable Cox proportional hazards analysis for RFS, T status, lymph node metastasis, HALP index, and lymphovascular invasion were identified as significant prognostic factors (Table III). In the multivariable Cox proportional hazards analysis for RFS, the HALP score was identified as an independent prognostic factor [odds ratio (OR)=1.852, 95% CI=1.197-2.866, *p*=0.006]. Similarly, T status and lymph node metastasis were also identified as significant prognostic factors in multivariable analysis.

*Comparison of the postoperative clinical course.* The rate of tumor recurrence in different sites was compared between the HALP-high and HALP-low groups (Table IV). The rate of hematological recurrence was found to be significantly higher in the HALP-low group than in the HALP-high group (34.5% *vs.* 17.1%, *p*=0.011) (Table IV).

Table II. *Univariable and multivariable Cox proportional hazards model for overall survival.*

| | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| Factors | n | HR | 95% CI | *p*-Value | HR | 95% CI | *p*-Value |
| Age (years) | | | | 0.535 | | | |
| <70 | 95 | 1.000 | | | | | |
| ≥70 | 85 | 1.160 | 0.727-1.851 | | | | |
| Sex | | | | 0.279 | | | |
| Female | 25 | 1.000 | | | | | |
| Male | 155 | 1.539 | 0.705-3.358 | | | | |
| T status | | | | **<0.001** | | | **0.014** |
| T1 | 79 | 1.000 | | | 1.000 | | |
| T2 or T3 | 101 | 3.473 | 2.012-5.995 | | 2.158 | 1.170-3.981 | |
| Lymph node metastasis | | | | **<0.001** | | | **0.037** |
| Negative | 58 | 1.000 | | | 1.000 | | |
| Positive | 122 | 2.644 | 1.625-4.302 | | 1.723 | 1.033-2.876 | |
| HALP index | | | | **0.004** | | | **0.012** |
| >40 | 70 | 1.000 | | | 1.000 | | |
| ≤40 | 110 | 2.162 | 1.284-3.640 | | 1.954 | 1.157-3.299 | |
| Lymph-vascular invasion | | | | **<0.001** | | | 0.075 |
| Negative | 35 | 1.000 | | | 1.000 | | |
| Positive | 145 | 3.243 | 1.742-6.037 | | 1.873 | 0.939-3.735 | |
| Tumor location | | | | 0.848 | | | |
| Middle, lower | 127 | 1.000 | | | | | |
| Upper | 53 | 1.051 | 0.631-1.750 | | | | |
| Postoperative complications | | | | 0.611 | | | |
| No | 53 | 1.000 | | | | | |
| Yes | 127 | 1.137 | 0.692-1.869 | | | | |

HALP: Hemoglobin, albumin, lymphocyte, platelet score; HR: hazard ratio; CI: confidence interval. Statistically significant *p*-values are shown in bold.

## Discussion

This study aimed to evaluate the usefulness of the HALP score as a prognostic factor in patients with EC who had undergone radical treatment, including surgery, and to consider how the HALP score can be utilized in clinical practice. We found significant differences in OS and RFS between the HALP-low and HALP-high groups, with the high HALP to be associated with better 5-year OS and 5-year RFS. In addition, the hematological recurrence rate was significantly higher in the HALP-low group than in the HALP-high group. Based on these results, we conclude that the HALP score has an impact on the long-term prognosis of patients with EC and that it can be used as a useful prognostic factor to assist in the perioperative treatment and management of patients with EC.

Several studies have reported the usefulness of the HALP score as a prognostic factor in patients with EC. In 2021, Feng *et al*. investigated whether preoperative HALP score could be a predictive factor for cancer-specific survival (CSS) in 355 patients with esophageal squamous cell carcinoma who underwent radical resection (21). In this study, the cutoff value for the HALP score was set at 31.8, with 172 patients in the HALP-low group and 183 patients in the HALP-high group. The 5-year CSS rate of the HALP-low group was significantly lower than that of the HALP-high group, respectively. The authors also conducted a subgroup analysis comparing CSS between the two groups for each TMN stage and sex. Regarding stage, for all TMN stages (I-III), the CSS rate was significantly higher in the HALP-high group than in the HALP-low group. In terms of sex, the CSS rate was also

Table III. *Univariable and multivariable Cox proportional hazards model for recurrence-free survival.*

| | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| Factors | No | HR | 95%CI | *p*-Value | HR | 95%CI | *p*-Value |
| Age (years) | | | | 0.885 | | | |
| <70 | 95 | 1.000 | | | | | |
| ≥70 | 85 | 1.030 | 0.689-1.539 | | | | |
| Sex | | | | 0.291 | | | |
| Female | 25 | 1.000 | | | | | |
| Male | 155 | 1.403 | 0.749-2.628 | | | | |
| T status | | | | **<0.001** | | | **<0.001** |
| T1 | 79 | 1.000 | | | 1.000 | | |
| T2 or T3 | 101 | 4.434 | 2.744-7.165 | | 2.789 | 1.642-4.737 | |
| Lymph node metastasis | | | | **<0.001** | | | 0.085 |
| Negative | 58 | 1.000 | | | 1.000 | | |
| Positive | 122 | 2.420 | 1.606-3.647 | | 1.456 | 0.949-2.234 | |
| HALP index | | | | **0.004** | | | **0.006** |
| >40 | 70 | 1.000 | | | 1.000 | | |
| ≤40 | 110 | 1.878 | 1.219-2.893 | | 1.852 | 1.197-2.866 | |
| Lymph-vascular invasion | | | | **<0.001** | | | **0.006** |
| Negative | 35 | 1.000 | | | 1.000 | | |
| Positive | 145 | 4.021 | 2.313-6.990 | | 2.334 | 1.273-4.277 | |
| Tumor location | | | | 0.840 | | | |
| Middle, lower | 127 | 1.000 | | | | | |
| Upper | 53 | 1.047 | 0.671-1.632 | | | | |
| Postoperative complications | | | | 0.785 | | | |
| No | 53 | 1.000 | | | | | |
| Yes | 127 | 1.062 | 0.690-1.634 | | | | |

HALP: Hemoglobin, albumin, lymphocyte, platelet score; HR: hazard ratio; CI: confidence interval. Statistically significant *p*-values are shown in bold.

significantly higher in the HALP-high group than in the HALP-low group for both males and females. From the above, it was found that the HALP score is a useful prognostic factor for CSS regardless of stage or sex. Furthermore, a multivariable analysis revealed that the HALP score could be an independent prognostic factor in patients with EC who underwent radical resection.

In 2021, Hu *et al*. also reported the usefulness of the HALP score in combination with maximum voluntary ventilation (MVV), a measure of the lung function, for predicting postoperative survival in patients with esophageal squamous cell carcinoma who underwent radical esophagectomy in 2021 (23). A total of 834 patients with esophageal squamous cell carcinoma underwent radical esophagectomy with R0 resection, and the cutoff value for the HALP score was set at 38.8. Regarding the correlation between the HALP score and clinical data, significant differences were found in tumor length and depth. In terms of the relationship between the HALP score and overall survival, a Kaplan-Meier analysis using a

Table IV. *Patterns of recurrence according to the HALP index.*

| | HALP index | | | | |
|---|---|---|---|---|---|
| | ≤40 (n=110) | | >40 (n=70) | | *p*-Value |
| Recurrence site | N | % | N | % | |
| Lymph node | 37 | | 20 | | 0.476 |
| Hematological | 38 | | 12 | | **0.011** |
| Local site | 19 | | 7 | | 0.176 |

HALP: Hemoglobin, albumin, lymphocyte, platelet score. Statistically significant *p*-values are shown in bold.

logrank test showed that a low HALP score was associated with a decrease in overall survival. A multivariable Cox regression analysis showed that the HALP score was an independent prognostic factor for OS. Although previous studies have demonstrated the prognostic value of HALP in various malignancies, in the present study, we showed the impact of the HALP score on the long-term postoperative clinical outcomes in EC patients.

There are two possible reasons that may explain the association of the HALP score with the long-term prognosis of EC patients who have undergone curative resection. One possibility is that the HALP score may be involved in the postoperative complications of the patients. Several studies have examined the relationship between HALP score and postoperative complications in patients with gastrointestinal cancer. In a study by Aoyama *et al*. that reported the value of the preoperative HALP score as a predictor in patients with gastric cancer who had undergone curative resection, the anastomotic leakage rate was higher in the HALP-low group than in the HALP-high group (24). In addition, Tazeoglu *et al*. reported the relationship between the HALP score and postoperative complications in patients with pancreatic cancer who underwent pancreaticoduodenectomy, the HALP-low group was reported to have significantly higher postoperative complications than the HALP-high group (25). Furthermore, they also reported that the HALP-low group had significantly higher rates of surgical site infection (SSI), bile leakage, and pancreatic leakage than the HALP-high group. Postoperative anastomotic leakage affects the postoperative survival prognosis of patients with gastrointestinal cancer (26). In this study, there was no significant difference between the two groups in terms of postoperative complications; however, a significant difference may have been detected in a larger cohort study.

The second reason is the rate of introduction of NAC. In this study, the rate of NAC introduction was higher in the HALP-high group than that in the HALP-low group. The usefulness of NAC treatment, in terms of outcomes, was proven in patients with resectable stage II-III EC in the JCOG 9970 trial (Japan Clinical Oncology) (27). In recent years, the addition of docetaxel to the cisplatin-5-FU (CF) regimen, which was previously the standard therapy, has been shown to prolong survival in JCOG1109 patients (28), and the usefulness of NAC in the treatment of EC is now widely recognized. When NAC is introduced, it suppresses the ability of tumor cells to divide, inhibits the invasion of tumor cells by subsequent surgery, and suppresses distant metastasis (27). In this study, the HALP-high group received NAC more frequently than the HLP-low group, which may have contributed to the higher OS and longer RFS rates.

*Study limitations.* First, it was conducted at a single facility; therefore, it was not possible to eliminate selective bias. In addition, patients in this study were treated between 2000 and 2020. During this period, the treatment methods for EC changed significantly with changes in NAC regimens and the introduction of robots for surgery, which may have affected OS and RFS. Third, the optimal cutoff value for the HALP score is unclear. In this study, the cutoff value for the HALP score was set at 40 based on the analysis of the overall survival rate. However, based on previous studies, the cutoff value for HALP varies. Hu *et al*. set the cutoff value for the HALP score at 38.8 for 834 patients with EC, and Feng *et al*. set the cutoff value at 31.8 for 355 EC patients. The differences in the cutoff values are thought to have arisen due to the differences in the number of patients, patient background factors, and treatment methods. To use the HALP score in the clinical setting, it will be necessary to set the optimal cutoff value. In the future, further large-scale cohort studies are warranted.

In conclusion, the HALP score may be a useful prognostic factor in patients with EC who have undergone radical resection. Therefore, the HALP score may be useful for the preoperative treatment and management of patients with EC.

## Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

## Authors' Contributions

SY and TA contributed substantially to study design. TA, YM, IH, SY, RE, KK, JM, SK, KS, MU, AT, and KN made substantial contributions to the data acquisition, analysis, and interpretation. TA, AS, and NY were involved in drafting and critically revising the manuscript for important intellectual content. TA and YM approved the final version of the manuscript.

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